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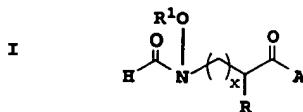
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N-FORMYL HYDROXYLAMINE CONTAINING COMPOUNDS
USEFUL AS ACE INHIBITORS AND/OR NEP INHIBITORS

Summary of the Invention

5 This invention is directed to novel compounds possessing angiotensin converting enzyme (ACE) inhibitory activity and/or neutral endopeptidase (NEP) inhibitory activity and methods of preparing such compounds. This invention is also directed to
10 pharmaceutical compositions containing such ACE and/or NEP inhibiting compounds or pharmaceutically acceptable salts thereof and the method of using such compositions.

The compounds of this invention are those of
15 the formula (I)



including a pharmaceutically acceptable salt thereof
where:

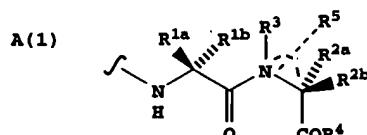
20 x is 0 or 1;
R is H, alkyl, alkenyl, aryl-(CH₂)_p-,
heteroaryl-(CH₂)_p-, cycloheteroalkyl-(CH₂)_p-, or
R can be joined together with the carbon to
which it is attached to form a 3 to 7 membered ring
25 which may optionally be fused to a benzene ring;

R¹ is H or -COR² where R² is alkyl, aryl-(CH₂)_p-, cycloheteroalkyl-(CH₂)_p-, heteroaryl-(CH₂)_p-, alkoxy, or cycloalkyl-(CH₂)_p;

p is 0 or an integer from 1 to 8; and

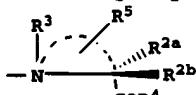
5 A is a dipeptide derived from one or two non-proteinogenic amino acid or is a conformationally restricted dipeptide mimic as described below.

A is a dipeptide derivative of the structure



where R^{1a}, R^{1b}, R^{2a} and R^{2b} are independently selected from H, alkyl, aryl-(CH₂)_p-, cycloalkyl, cycloheteroalkyl-(CH₂)_p-, heteroaryl-(CH₂)_p-, biphenylmethyl, or

15 R^{1a} and R^{1b} or R^{2a} and R^{2b} may be joined together to the carbon to which they are attached to form a 3 to 7 membered ring, optionally fused to a



benzene ring; and COR⁴ refers to an optional 5 or 6 membered ring containing a single hetero atom and which may optionally include an R⁵ substituent (as shown) which is H, alkyl, aryl-(CH₂)_p or cycloalkyl-(CH₂)_p, cycloheteroalkyl-(CH₂)_p, or cycloheteroaryl-(CH₂)_p;

R³ is H, alkyl or aryl -(CH₂)_p-;

25 R⁴ is OH, Oalkyl, O-(CH₂)_paryl- or NR₁(R₂) where R₁ and R₂ are independently H, alkyl, or aryl(CH₂)_p or heteroaryl-(CH₂)_p;

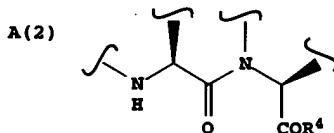
with the proviso that in A(1) at least one of

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is other than a natural α -amino acid, and thus must be other than valine, leucine, phenylalanine, tyrosine, serine, cysteine, threonine, methionine, 5 aspartic acid, glutamic acid, arginine, lysine or proline.

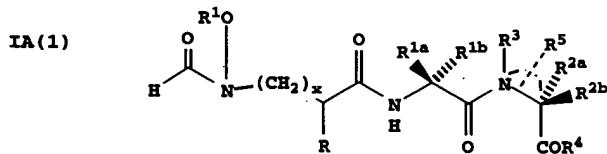
In addition, A can be a conformationally restricted dipeptide mimic which has the structure



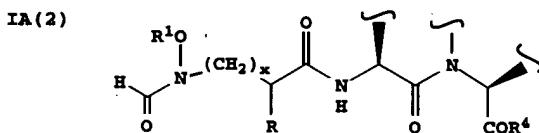
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and is a non-proteinogenic dipeptide.

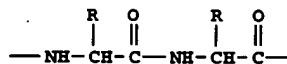
Thus, the compound of formula I include



15 and



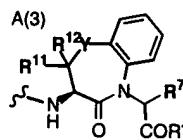
The term "conformationally restricted
20 dipeptide mimic" refers to a structural skeleton which has the attributes of a conventional dipeptide



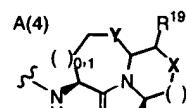
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but having enhanced biological properties due to additional bonds which limit the rotational freedom.

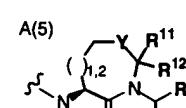
Examples of the A(2) dipeptide mimics include any of the conformationally restricted dipeptide mimics set out below.



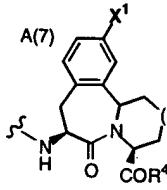
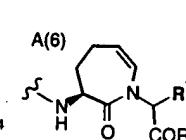
where $Y = O, S, \text{CH}_2$
or $S(O)_{0,1,2}$



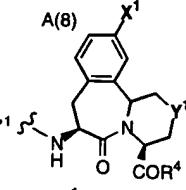
where $X = \text{CH}_2$ and
 $Y = O, S, \text{CH}_2$ or $S(O)_{0,1,2}$
and $X = O, S$ when $n = 1$



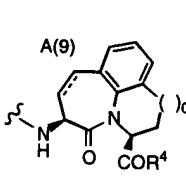
where $Y = O, S, \text{CH}_2$
or $S(O)_{0,1,2}$



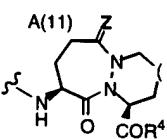
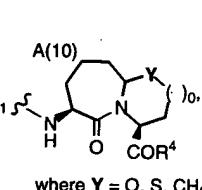
where $X^1 = H, \text{Ph},$
 NHSO_2R^5
(R^5 H)



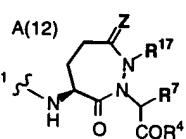
where $Y^1 = O, S, \text{NH}$
or $S(O)_n$,
where $X^1 = H, \text{Ph},$
 NHSO_2R^5
(R^5 H)



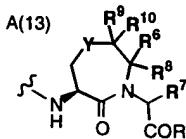
where $Y = O, S, \text{CH}_2$
or $S(O)_{0,1,2}$



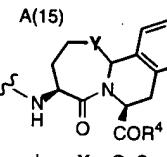
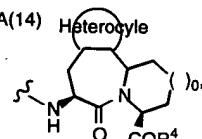
where $Z = O$ or H, H



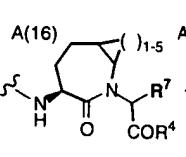
where $Z = O$ or H, H



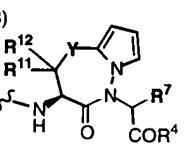
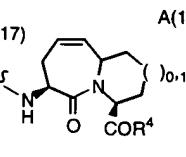
where $Y = O, S, \text{CH}_2$
or $S(O)_{0,1,2}$



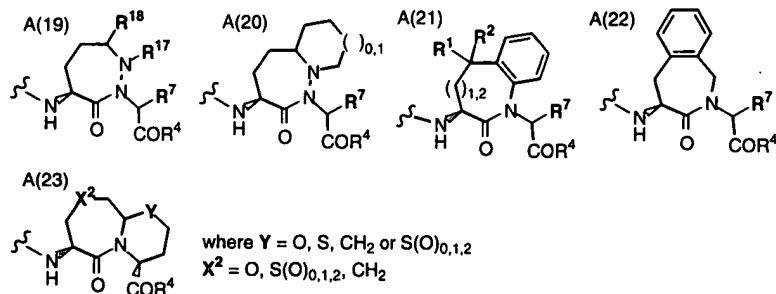
where $Y = O, S,$
or $S(O)_{0,1,2}$



where $Y = O, S,$
or $S(O)_{0,1,2}$

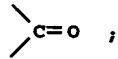


where $Y = O, S, \text{CH}_2$



With respect to A(5), R¹¹ and R¹² are

independently selected from hydrogen, alkyl,
5 substituted alkyl, alkenyl, substituted alkenyl,
cycloalkyl -(CH₂)_m-, aryl -(CH₂)_m-, substituted aryl
-(CH₂)_m-, and heteroaryl -(CH₂)_m-, or R¹¹ and R¹²
taken together with the carbon to which they are
attached complete a saturated cycloalkyl ring of 3 to
10 7 carbons, or R¹¹ and R¹² taken together with the
carbon to which they are attached complete a keto
substituent, i.e.,

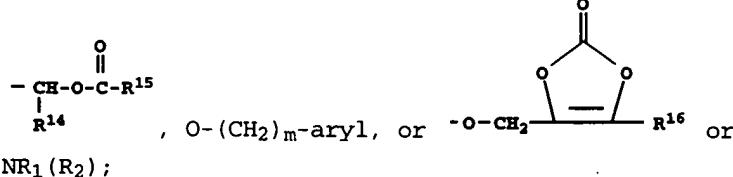


with respect to A(13) R⁸, R⁹ and R⁷ are

15 independently selected from hydrogen, alkyl,
substituted alkyl, alkenyl, substituted alkenyl,
cycloalkyl -(CH₂)_m-, aryl-(CH₂)_m-, substituted aryl-
(CH₂)_m-, and heteroaryl-(CH₂)_m;
R¹⁰ and R⁶ are independently selected from
20 hydrogen, alkyl, substituted alkyl, alkenyl,
substituted alkenyl, cycloalkyl -(CH₂)_m-, aryl-
(CH₂)_m, substituted aryl -(CH₂)_m-, and heteroaryl-
(CH₂)_m, or R⁶ and R¹⁰ taken together with the carbon
to which they are attached complete a saturated
25 cycloalkyl ring of 3 to 7 carbons, R⁶ and R⁸ taken
together with the carbon to which they are attached

complete a saturated cycloalkyl ring of 3 to 7 carbons, or R⁹ and R¹⁰ taken together with the carbon to which they are attached complete a saturated cycloalkyl ring of 3 to 7 carbons;

5 m is zero or an integer from 1 to 6;
 R⁴ is OH, Oalkyl, O-(CH₂)_m-heteroaryl,



where R₁ and R₂ are independently H, alkyl, aryl(CH₂)_p, aryl or heteroaryl;
 10 R¹⁴ is hydrogen, lower alkyl, cycloalkyl, or phenyl;
 R¹⁵ is hydrogen, lower alkyl, lower alkoxy or phenyl;
 15 R¹⁶ is alkyl or aryl-(CH₂)_m-; and
 R¹⁷ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl-(CH₂)_m-, aryl-(CH₂)_m-, substituted aryl-(CH₂)_m-, or heteroaryl-(CH₂)_m.
 20 R¹⁸ is H, alkyl or alkenyl, and R¹⁸ and R¹⁷ may be taken together with the carbon and nitrogen to which they are attached to complete a saturated N-containing ring of 5 or 6 ring members.

R¹⁹ is H or an alkyl, and in A(4), R¹⁹ and X (which is CH₂) together with the carbons to which they are attached may form an aromatic ring of carbons (as in A(15)).

The starting compounds H-A(1) and H-A(2) are described in the literature or are obtained by modifications of known procedures. For example, the

starting compounds of formula H-A(1) or H-A(2)
wherein A(1) or A(2) is as defined in formulas A(5),
A(13), A(16), A(21), where Y (where present) is CH₂
are disclosed by Thorsett et al., J. Med. Chem., 29,

5 p. 251 - 260 (1988), Harris et al. in U.S. Patents
4,587,050, 4,587,238, 4,629,787 and Yanagisawa et al.
in U.S. Patent 4,734,410.

The starting compounds of formula H-A(1) or H-
A(2) wherein A(1) or A(2) is as defined in formulas
10 A(3) and A(13) where Y is S(O)n are disclosed by
Yanagisawa et al., J. Med. Chem., 30, p. 1984 - 1991
(1987) and 31, p. 422 - 428 (1988), Karanewsky in
U.S. Patent 4,460,579, Cheung et al. in U.S. Patent
4,594,341, and Yanagisawa et al. in U.S. Patent
15 4,699,905.

The starting compounds of formula H-A(1) or H-
A(2) wherein A(1) or A(2) is as defined in formula
A(5) are disclosed by Karanewsky in U.S. Patents
4,460,579 and 4,711,884.

20 The starting compounds of formula H-A(1) or H-
A(2) wherein A(1) or A(2) is as defined in formulas
A(3) (Y is -CH₂-, and A(21) are disclosed by Watthey
et al., J. Med. Chem., 28, p. 1511 - 1516 (1985) and
Watthey in U.S. Patents 4,410,520, 4,470,988,
25 4,473,575, 4,537,885 and 4,575,503 and also by
Parsons et al., Biochemical & Biophysical Research
Comm., 117, p. 108 - 113 (1983) and in U.S. Patent
4,873,235.

The starting compounds of formula H-A(1) or H-
30 A(2) wherein A(1) or A(2) is as defined in formula
A(3) and Y is S or O are disclosed by Slade et al.,
J. Med. Chem., 28, p. 1517 - 1521 (1985) and in U.S.
Patent 4,477,464 and Itoh et al., Chem. Pharm. Bull.,
34, p. 1128 - 1147 (1986) and 34, p. 2078 - 2089

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(1986) as well as Sugihara et al. in U.S. Patent 4,548,932 (Y is O) and Katakami et al. in U.S. Patent 4,539,150 (Y is S).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(16) can be prepared by reduction of the corresponding starting compounds wherein A(1) or A(2) is as defined in formula A(3).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(22) are disclosed by Flynn et al in U.S. Patent 4,973,585.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(10) and Y is S, -SO, or -SO₂ are disclosed by Harris et al. and Patchett et al. in U.S. Patents 4,415,496 and 4,617,301.

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(10) and Y is CH₂, and is as defined in formula A(23) where X² is CH₂ is disclosed by Thorsett, Actual. Chim. Ther., 13, p. 257-268 (1986).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formulas A(11) and A(19) and A(20) are disclosed by Attwood et al., Federation of European Biochemical Studies, 165, p. 201-206 (1984) and in U.S. Patent 4,512,994 and Natoff et al., Drugs Of The Future, 12, p. 475-483 (1987).

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(12) are disclosed by Huang et al. in U.S. Patent 4,465,679.

CONFIDENTIAL SOURCE

The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(18) are disclosed by Bolos et al. in Tetrahedron, 48, p. 9567-9576 (1992).

5 The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formulas A(4) and A(15) are disclosed in European Patent Application 0629627A2.

10 The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(9) are disclosed in U.S. application Serial No. 100,408 (file HA611a).

15 The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formulas A(7) and A(8) are disclosed in European Patent Application 481,522 (Flynn et al) and European Patent Application 0534363A2 (Warshawsky et al).

20 The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(14) are disclosed in U.S. application Serial No. 153,854 (file HA615).

25 The starting compounds of formula H-A(1) or H-A(2) wherein A(1) or A(2) is as defined in formula A(17) are disclosed in European Patent Application 0599444A1 (Barrish et al).

30 In addition, in accordance with the present invention, a pharmaceutical composition is provided which includes a therapeutically effective amount of compound I and a pharmaceutically acceptable carrier therefor.

 The pharmaceutical composition as defined above will be useful in the treatment of cardiovascular diseases such as hypertension and/or congestive heart failure.

CONFIDENTIAL

Furthermore, in accordance with the present invention, a method is provided for treating a cardiovascular disease such as hypertension and/or congestive heart failure, as well as other diseases 5 as set out hereinafter, which includes the step of administering to a mammalian species, including humans, dogs and cats, a therapeutically effective amount of a composition as defined above.

10 Detailed Description Of The Invention

The term "alkyl" or "lower alkyl" refers to straight or branched chain radicals having up to and including ten carbon atoms, preferably up to and including six carbon atoms, which may optionally 15 include one, two, or three substituents including a hydroxy, amino, alkyl, cycloalkyl, aryl, halo, trifluoromethyl, cyano, -NH(lower alkyl), -N(lower alkyl)₂, lower alkoxy, lower alkylthio, carboxy or heteroaryl.

20 The term "alkenyl" refers to straight or branched chain radicals of 3 to 10 carbon atoms having one or two double bonds, preferably straight chain radicals of 3 to 5 carbons having one double bond, which may optionally be substituted with one, 25 two or three substituents including alkyl, aryl, cycloalkyl, hydroxy, amino, halo, trifluoromethyl, cyano, -NH(lower alkyl), -N(lower alkyl)₂, lower alkoxy, lower alkylthio, carboxy or heteroaryl.

25 The terms "alkoxy" or "lower alkoxy" and 30 "alkylthio" or "lower alkylthio" refer to such alkyl groups as defined above attached to an oxygen or sulfur.

30 The term "cycloalkyl" refers to saturated rings of 3 to 7 carbon atoms.

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The term "halo" refers to chloro, bromo, fluoro, and iodo.

The term "aryl" refers to aromatic groups containing 6 to 10 carbons, preferably phenyl, 1-naphthyl, and 2-naphthyl, which may optionally contain one, two or three substituents selected from alkyl, alkoxy, alkylthio, halo, hydroxy, trifluoromethyl, $-SO_2NH_2$, amino, $-NH(lower\;alkyl)$, or $-N(lower\;alkyl)_2$, di- and tri-substituted phenyl, 1-naphthyl, or 2-naphthyl, wherein said substituents are preferably selected from methyl, methoxy, methylthio, halo, hydroxy, and amino.

The term "heteroaryl" refers to unsaturated rings of 5 or 6 atoms containing one or two O and S atoms and/or one to four N atoms provided that the total number of hetero atoms in the ring is 4 or less, which may optionally be substituted with one, two or three substituents which include alkyl, aryl, cycloalkyl, alkoxy or halo. The heteroaryl ring is attached by way of an available carbon or nitrogen atom. Preferred heteroaryl groups include 2-, 3-, or 4-pyridyl, 4-imidazolyl, 4-thiazolyl, 2- and 3-thienyl, and 2- and 3-furyl. The term heteroaryl also includes bicyclic rings wherein the five or six membered ring containing O, S, and N atoms as defined above is fused to a benzene or pyridyl ring. Preferred bicyclic rings are 2- and 3-indolyl and 4- and 5-quinolinyl. The mono or bicyclic heteroaryl ring can also be additionally substituted at an available carbon atom by a lower alkyl, halo, hydroxy, benzyl, or cyclohexylmethyl. Also, if the mono or bicyclic ring has an available N-atom such N atom can also be substituted by an N-protecting group such as .

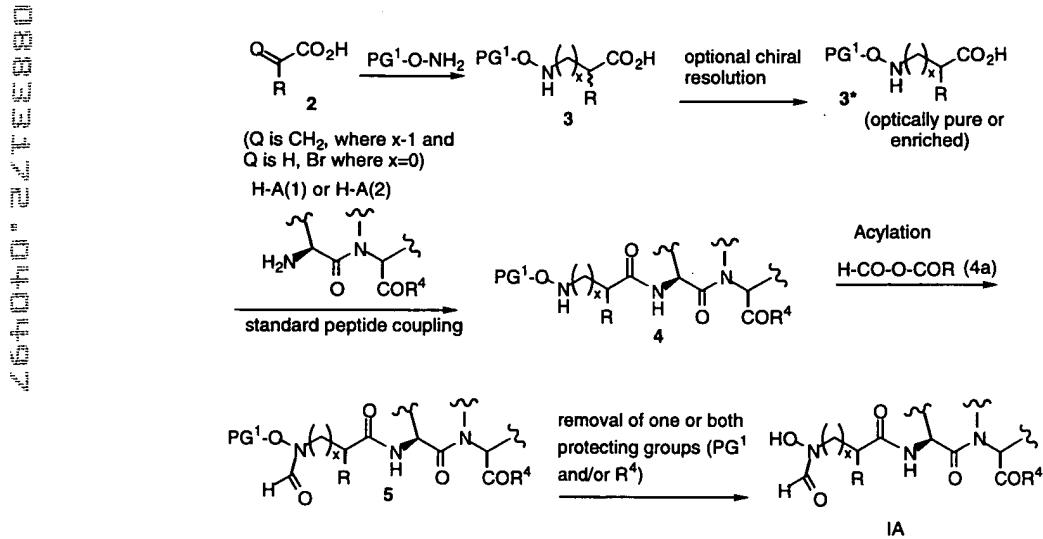
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2,4-dinitrophenyl, lower alkyl, benzyl, or
5 benzhydryl.

The compounds of formula I of the invention may be prepared as outlined in Reaction Scheme I set out below (where x is 0 or 1).

10 Reaction Scheme I

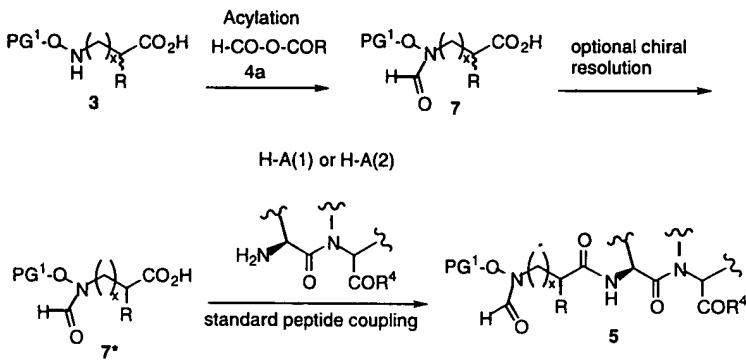


As shown in Scheme I, acid 2 may be reacted
15 with a suitably O-protected (e.g. PG¹ is benzyl, p-methoxybenzyl, tetrahydropyranyl, trityl, benzhydryl, etc.) hydroxylamine to give the adduct 3. Compound 3 may be coupled directly with amine H-A(1) or H-A(2) to give a mixture of diastereomers which may be
20 separated or preferably compound 3 may be optically enriched or purified, employing conventional

techniques, to give 3*. Subsequent coupling with H-A(1) or H-A(2) gives 4 in diastereomerically enriched or pure form. Reaction of the hydroxylamine nitrogen of 4 with a formylating agent affords 5. At 5 this point one or both protecting groups may be removed, either sequentially or simultaneously, to produce compound of the invention IA. For example, when PG¹ is benzyl and R⁴ is Obenzyl, both may be removed by hydrogenolysis. When PG¹ is benzyl and R⁴ 10 is -Omethyl or -Oethyl, the PG¹ group may be removed by hydrogenolysis and the ester group may be converted to the acid by base hydrolysis. PG¹ groups such as THP or trityl may be removed by treatment 15 with strong acid such as hydrogen chloride or trifluoro acetic acid in a protic solvent.

Alternately, compounds of the invention IA may be obtained by the route depicted in Scheme II (where x is 0 or 1).

20 Reaction Scheme II



As seen in Reaction Scheme II, compound **3** may
25 be formylated with an formylating agent **4a** to give
acid compound **7**. This acid may be coupled with **A(1)**

or A(2) directly or optically resolved to give 7* and then coupled to give compound 5. Compound 5 is then converted to compound of the invention IA as described above.

- 5 The compounds of formula I of the invention contain one or more asymmetric centers. Thus, these compounds can exist in diastereoisomeric forms or in mixtures thereof and all of such forms are within the scope of this invention. The above described
- 10 processes can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric compounds are prepared, they can be separated by conventional chromatographic or fractional crystallization methods.
- 15 The compounds of formula I of the invention can be isolated in the form of a pharmaceutically acceptable salt. Suitable salts for this purpose are alkali metal salts such as sodium and potassium, alkaline earth metal salts such as calcium and
- 20 magnesium, and salts derived from amino acids such as arginine, lysine, etc. These salts are obtained by reacting the acid form of the compound with an equivalent of base supplying the desired ion in a medium in which the salt precipitates or in aqueous
- 25 medium and then lyophilizing.

The compounds of formula I of the invention are inhibitors of angiotensin converting enzyme and/or neutral endopeptidase. Thus, the compounds of formula I including their pharmaceutically acceptable salts are useful in the treatment of physiological conditions in which either angiotensin converting enzyme inhibitors or neutral endopeptidase inhibitors have been shown to be useful. Such conditions include cardiovascular diseases, particularly,

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hypertension, congestive heart failure, renal failure, and hepatic cirrhosis, as well as analgesic activity. The compounds of formula I are also inhibitors of other metalloproteases such as the

5 matrix metalloproteases, for example, gelatinase, collagenase and stromelysin and thus are useful in the treatment of osteoarthritis, rheumatoid arthritis, metastatic tumors, and angiogenesis.

Diuresis, natriuresis, and blood pressure reduction are produced in a mammalian host such as man by the administration of from about 1 mg. to about 100 mg. per kg. of body weight per day, preferably from about 1 mg. to about 50 mg. per kg. of body weight per day, of one or more of the 10 compounds of formula I or a pharmaceutically acceptable salt thereof. The compounds of formula I are preferably administered orally, but parenteral routes such as subcutaneous, intramuscular, and intravenous can also be employed. The daily dose can 15 be administered singly or can be divided into two to four doses administered throughout the day.

The ACE and/or NEP inhibitors of formula I can be administered in combination with human ANF 99 - 126. Such combination would contain the inhibitor of 20 formula I at from about 1 to about 100 mg. per kg. of body weight and the human ANF 99 - 126 at from about 0.001 to about 0.1 mg. per kg. of body weight.

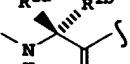
The ACE and/or NEP inhibitors of formula I can be administered in combination with other classes of 25 pharmaceutically active compounds. For example, a calcium channel blocker, a potassium channel activator, a cholesterol reducing agent, etc.

The ACE and/or NEP inhibitors of formula I or a pharmaceutically acceptable salt thereof and other

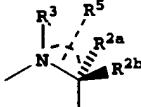
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pharmaceutically acceptable ingredients can be formulated for the above described pharmaceutical uses. Suitable compositions for oral administration include tablets, capsules, and elixirs, and suitable 5 compositions for parenteral administration include sterile solutions and suspensions. About 10 to 500 mg. of active ingredient is compounded with physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavoring, etc., in 10 a unit dose form as called for by accepted pharmaceutical practice.

Preferred compounds of the invention are those of formula I wherein

15 R¹ is H,
 x is 1,
 R is alkyl or arylalkyl, and
 A is A(1), preferably

 where  is preferably a non-proteinogenic amino acid portion wherein,
 R^{1a} and R^{1b} are each independently alkyl such as methyl or ethyl, or arylalkyl such as benzyl, or
 R^{1a} and R^{1b} together with the carbon to which they are attached form a 3-7 membered ring, preferably a 5-membered ring, or
 25 R^{1a} and/or R^{1b} is biphenylmethylene and the other may be H.

Also preferred are compounds where A is A(1),



preferably where  and is a non-proteinogenic amino acid where R³ is H, alkyl, such as methyl

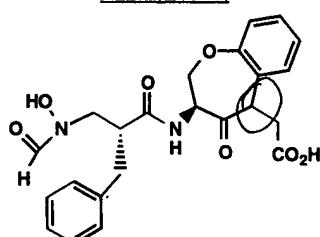
or ethyl, aryl such as phenyl, or arylalkyl, such as benzyl,

R^{2a} and R^{2b} are independently selected from H, alkyl, aryl, arylalkyl (with at least one of R^{2a} and R^{2b} being other than H) or R^{2a} and R^{2b} together with the carbon to which they are attached form a 3-7 membered ring, preferably 5- or 6-membered ring.

Also preferred are compounds where A is A(2) wherein R⁴ is OH.

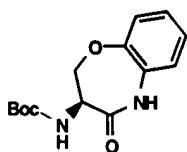
10 The following Examples represent preferred embodiments of the present invention.

Example 1

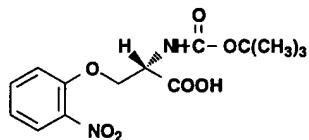


15

A.



A(1).



20

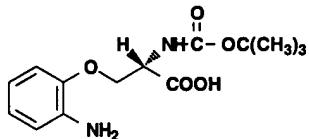
A solution of BOC-L-serine (24.3 g, 0.118 mole) in dry dimethylformamide (25 ml) was added dropwise over a period of 1.0 hour to a cooled (0°,

ice-salt bath) suspension of 60% NaH (10.1 g, 0.25 mole) in dry dimethylformamide (200 ml) and stirring was continued at 0° until the frothing subsided (ca. 2.0 hours). The reaction mixture was treated

5 dropwise with 1-fluoro-2-nitrobenzene (14.3 ml, 0.13
mole) over a period of 20 minutes, stirred at 0°
under argon for 4.0 hours then poured into ice-water
(750 ml) and extracted with Et₂O (2 x 100 ml). The
aqueous phase was brought to pH 1.0 with 6 N HCl (70
10 ml), extracted with EtOAc (3 x 500 ml) and the
combined organic extracts were washed with brine (100
ml), dried (anhydrous Na₂SO₄), filtered, evaporated
to dryness and dried *in vacuo*. The crude product
mixture was chromatographed on a silica gel column
15 (Merck), eluting the column with CH₂Cl₂:CH₃OH:HOAc
(100:5:0.2) to give title compound as a thick yellow
syrup (27.222 g, 70.7%) with consistent ¹H-NMR and
¹³C-NMR spectral data. TLC: R_f 0.27 (Silica gel;
CH₂Cl₂:CH₃OH:HOAc- 100:5:0.5; UV, PMA).

20

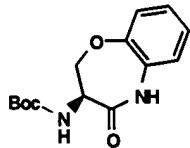
A(2).



A solution of Part A(1) compound (27.1 g, 83
25 mmoles) in dry methanol (500 ml) was treated with 10%
Pd/C (900 mg) and hydrogenated at 40 psi for 2.0
hours. The reaction mixture was filtered through a
Celite® pad in a millipore unit, washing the pad well
with CH₃OH (5 x 100 ml). The dark filtrate was
30 evaporated to dryness and dried *in vacuo* to give a
dark solid. The crude product was triturated with
CH₂Cl₂:Hexane (1:4) to give title compound as a light

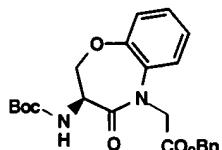
tan solid (17.69 g, 71. %) with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. TLC: R_f 0.15 (Silica gel; $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}:\text{HOAc}$ - 20:1:1; UV).

5 A(3).



A solution of Part A(2) compound (16.69 g, 56.3 mmoles) in dry dimethylformamide (121 ml) was
 10 treated with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (10.64 g, 55.5 mmoles) and stirred at room temperature for 3.0 hours. The reaction mixture was partitioned between EtOAc (2 x 492 ml) and 1.0 N NaHCO_3 (492 ml), and the combined organic extracts
 15 were washed with H_2O (3 x 492 ml), brine (492 ml), dried (anhydrous MgSO_4), filtered, evaporated to dryness and dried in vacuo. The crude product was chromatographed on a silica gel column (Merck), eluting the column with EtOAc:Hexane mixtures (1:4; 1:2; 1:1) to give title compound as off-white crystals (10.5 g, 72.4%) with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. TLC: R_f 0.40 (Silica gel; EtOAc:Hexane- 1:4; UV).

25 B.

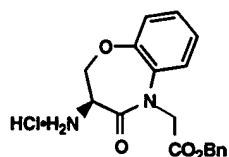


A solution of Part A compound (640 mg, 2.30 mmol) in dry THF (12 mL) at 0°C was treated with

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LiN(TMS)2 (1.0 M in THF, 2.60 mL, 2.60 mmol) followed approximately 30 seconds later with benzyl bromoacetate (475 μ L, 687 mg, 3.0 mmol). After 25 minutes, the mixture was quenched with saturated NH₄Cl, diluted with H₂O, and extracted with EtOAc. The EtOAc extract was washed with H₂O and brine, then dried (Na₂SO₄), filtered and stripped to give a yellow oil. Flash chromatography (Merck SiO₂, 3/7-EtOAc/hexanes as eluant) provided title compound (967 mg, 98%) as a colorless oil/foam.

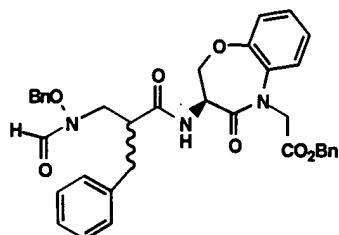
C.



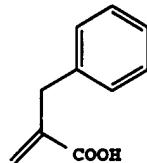
A solution of Part B compound (960 mg, 2.25 mmol) in 1,4-dioxane (4 mL) was treated with a solution of 4.0 M HCl in 1,4-dioxane (6 mL) at room temperature. After 3 hours, the mixture was concentrated in vacuo, triturated with Et₂O to give a solid and stripped to afford title compound (858 mg, 105% of theory).
m.p. 152-155°C.

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SPECTROSCOPY

D.



D(1).



5

A solution of benzylmalonic acid (23.06 g, 0.12 mole) in H₂O (200 mL) was treated with 37% CH₂O solution (278.4 mL) and 40% aqueous (CH₃)₂NH (35 mL,

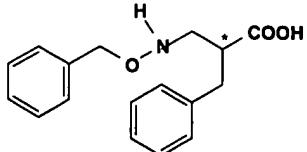
10 0.31 mole) then stirred overnight at room temperature under argon. The clear solution was heated to an internal temperature of 90°C for 2.0 hours (at which time gas evolution had ceased), cooled and acidified to pH 1.0 with 12 N HCl (20 mL). The white

15 precipitates were filtered off, washed with H₂O (3 x 25 mL) and dried in vacuo to give title compound as a white solid (12.85 g, 66.6%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.63 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV). m.p. 66-68°C.

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D(2).

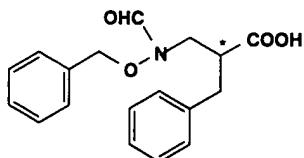


(J. Med. Chem. 28, 1985, 1167)

5 A solution of Part D(1) compound (8.9 g, 54.9
mmoles) and O-benzylhydroxylamine (26.7 g, 0.23 mole)
in absolute EtOH (9.0 ml) was refluxed for 7 days,
cooled to room temperature and evaporated to dryness.
The residual syrup was dissolved in 1.0 N NaOH (55
ml), stirred for 15 minutes then extracted with EtOAc
(4x 18 ml). The organic phase was washed with H₂O (3
x 10 ml) and the aqueous extracts were combined and
acidified to pH 2.0 with 1.0 N HCl (62 ml). The
acidic aqueous phase was then extracted with EtOAc (5
15 x 75 ml) and the combined organic extracts washed
with H₂O (2 x 30 ml), dried (anhydrous Na₂SO₄),
filtered, evaporated to dryness and dried in vacuo.
The crude product (3.93 g, 25.1%) was triturated with
Et₂O:Hexane (1:4; 2 x 25 ml) and all solids obtained
20 were dissolved in CH₂Cl₂ and filtered, washing the
insoluble precipitates with CH₂Cl₂. The clear
filtrate was evaporated and dried in vacuo to give
the title compound as an opaque colorless solid with
consistent ¹H-NMR and ¹³C-NMR spectral data.
25 TLC: R_f 0.33 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV, PMA).
M.p. 69-71°C.

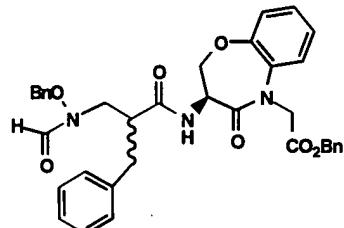
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D(3).



A cooled (0°C , ice-salt bath) mixture of HCOOH
 5 (17.5 ml) and acetic anhydride (Ac_2O) (1.75 ml) was
 stirred for 20 minutes, treated with Part D(2)
 compound (1.0 g, 3.5 mmoles) and stirring was
 continued at 0°C for another 3.0 hours. The reaction
 mixture was stripped to dryness, evaporated from Et_2O
 10 (2 x 25 ml), toluene (20 ml) and hexane (2 x 50 ml)
 then dried *in vacuo* to give title compound as a thick
 syrup (1.096 g, 100% crude yield) with consistent
 $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. TLC: R_f 0.23
 (Silica gel; $\text{CH}_2\text{Cl}_2:\text{MeOH}$ - 9:1; UV, PMA).
 15

D(4).



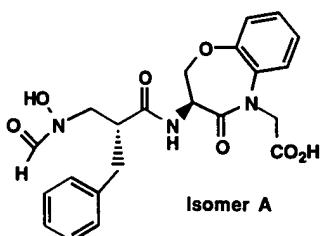
A solution of Part D(3) compound (366 mg, 1.19
 20 mmol) in CH_2Cl_2 (9 mL) at 0°C was treated with HOBT
 hydrate (210 mg) followed by EDAC (230 mg, 1.20
 mmol). After 20 minutes, the mixture was treated
 with Part C amine hydrochloride 3 (390 mg, 1.07 mmol)
 followed by 4-methylmorpholine (200 μL , 184 mg, 1.8
 25 mmol). The mixture was stirred at 0°C for 1 hour and
 at room temperature for 2 hours. The reaction was

REAGENTS AND EQUIPMENT

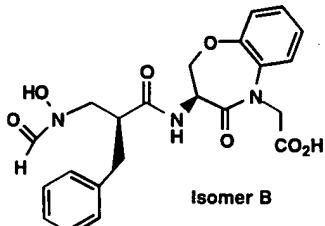
partitioned between EtOAc and 5% KHSO₄. The EtOAc extract was washed successively with H₂O, 50% saturated NaHCO₃ and brine, then dried (Na₂SO₄).

5 SiO_2 , 50% to 60% EtOAc in hexanes as eluant) provided title compound (550 mg, 84%) as a white foam which was shown by NMR and HPLC to be a 1:1 mixture of diastereomers.

10 E.



A solution of Part D compound (535 mg, 0.87 mmol) in MeOH (10 mL) was hydrogenated (balloon) over 15 10% Pd/C (123 mg) at room temperature for 2.75 hours. The solvent was filtered through Celite and the filtrate was stripped to give a diastereomeric mixture of title Isomer A and Isomer B.



. Trituration of a solution
20 of the residue in MeOH with Et₂O provided 350 mg of the diastereomeric mixture. Approximately 255 mg of this mixture was separated by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate 25 mL/min detecting at 220 nm; 40 to 100% B over a 30 minute

linear gradient (solvent A: 90% H₂O-10% MeOH-0.1% TFA; solvent B: 10% H₂O-90% MeOH-0.1% TFA); title Isomer A t_R = 14.4 min; separation performed in three runs).

5 The desired fractions were stripped, azetroped with EtOAc, re-dissolved in EtOAc and triturated with Et₂O to give title Isomer A (105.5 mg) as an off-white solid.

MS: (M+NH₄)⁺ 459; (M-H)⁻ 440

10

HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.2% H₃PO₄; solvent B: 0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R=9.67 min (96.0%).

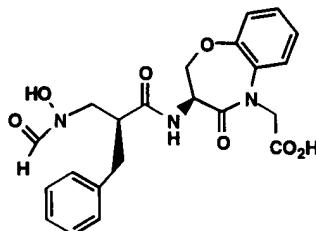
15 Anal. Calc'd for C₂₂H₂₃N₃O₇•1.6H₂O•0.1EtOAc•0.1Et₂O

C, 56.29; H, 5.80; N, 8.64

Found: C, 56.21; H, 5.15; N, 8.29.

20

Example 2



25 A solution of Example 1 Part E Isomers A and B (1:1 mixture of diastereomers, 535 mg, 0.87 mmol) in MeOH (10 mL) was hydrogenated (balloon) over 10% Pd/C (123 mg) at room temperature for 2.75 hours. The solvent was filtered through Celite and the filtrate

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was stripped to give a diastereomeric mixture of Isomers A and B. Trituration of a solution of the residue in MeOH with Et₂O provided 350 mg of the diastereomeric mixture. Approximately 255 mg of this

5 mixture was separated by preparative HPLC (YMC S5 ODS 30 x 250 mm column; flow rate 25 mL/min detecting at 220 nm; 40 to 100% B over a 30 minute linear gradient (solvent A: 90%H₂O-10% MeOH-0.1% TFA ; solvent B: 10% H₂O-90% MeOH-0.1% TFA); Isomer B t_R = 18.6 min;

10 separation performed in three runs). The desired fractions were stripped, azetroped with EtOAc, re-dissolved in EtOAc and triturated with Et₂O to give Isomer B (88.0 mg) as an off-white solid.

15 MS: (M+NH₄)⁺ 459; (M-H)⁻ 440

HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90%H₂O-10% MeOH-0.2%

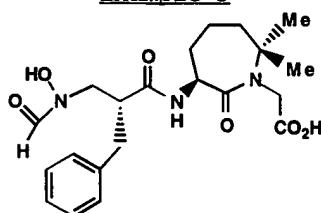
20 H₃PO₄; solvent B:0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R = 13.8 min (94.0%).

Anal. Calc'd for C₂₂H₂₃N₃O₇•1.5H₂O•0.2Et₂O

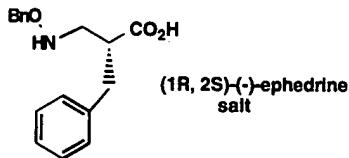
C, 56.66; H, 5.84; N, 8.69

25 Found: C, 56.84; H, 5.22; N, 8.42.

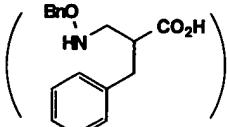
Example 3



A.



A solution of Example 1 Part D(1) compound

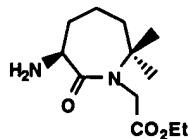


5 (2.563 gm, 8.98 mmol) in CH₃CN (20
 mL) was treated with (1R,2S)-(-)-ephedrine (1.522 gm,
 9.2 mmol) and stirred until homogeneous. Most of the
 solvent was removed by rotary evaporation and the
 residue was dissolved in Et₂O (25 mL) and treated
 10 with hexane (16 mL) in portions until the mixture was
 slightly turbid. The solution was seeded and let
 stand overnight at room temperature. The precipitate
 was collected by filtration and rinsed with 1:1
 Et₂O:hexanes and dried to afford 2.101 gm of white
 15 crystals ([a]_D = -16.4° (c 0.6, CH₂Cl₂)). The solid
 (2.087 gm) was dissolved in CH₂Cl₂, concentrated and
 diluted with Et₂O (18 mL) and hexane (8 mL) and
 seeded. The precipitate was collected by filtration
 and washed with 1:1-Et₂O:hexanes followed by hexanes
 20 to give title compound (1.995 gm) which was
 diastereomerically enriched in one isomer but not
 diastereomerically pure ([a]_D = -17.0° (c 0.6,
 CH₂Cl₂)).

25 mp 110-114°C
Material suitable for x-ray crystallographic analysis
was obtained by repeated recrystallization of the
solid from CH₃CN. mp 117-119°C;

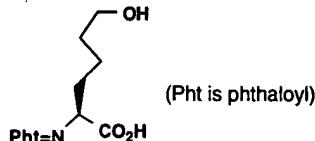
($[\alpha]_D = -19.7^\circ$ (c 0.4, CH_2Cl_2)).

B.



5

B(1).



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To a stirred solution of L-(+)-hydroxynor-

10 leucine (75 g, 509.6 mmole) and sodium carbonate (54 g, 509.6 mmole) in water (900 ml) at room temperature under argon was treated with N-ethoxy-carbonyl-phthalimide (111.7 g, 509.6 mmole). After being stirred for 2.0 hours, the resulting solution was

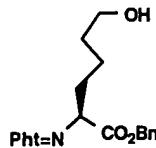
15 filtered through a pad of celite. The filtrate was cooled in an ice bath and carefully acidified to pH=3 with 6N HCl solution. The white solid which had precipitated was filtered and dried over P_2O_5 in vacuo to afford Compound 1 (124.5 g) in 88.1% yield.

20

M.P. 162°C

$\text{H}^1\text{-NMR}$ (DMSO): $\delta = 1.32$ (m, 6H), 2.13 (m, 2H), 4.38 (s, OH), 5.75 (m, 1H), 7.92 (m, 4H) ppm

B(2).

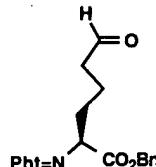


To a stirred slurry of Part B(1) compound
 5 (124.5 g, 0.449 mole) and cesium carbonate (73.2 g,
 0.225 mole) in DMF (1.25 L) at room temperature under
 argon was added benzyl bromide (98.4 g, 0.575 mole).
 After 2.5 hours, the resulting solution was poured
 into EtOAc (3.0 L), washed with water (3X), 5% LiCl
 10 solution and brine, dried over anhydrous Mg₂SO₄ and
 evaporated in vacuo to afford title compound (142 g)
 as an oil in 86.1% yield.

¹H-NMR (CDCl₃): δ = 1.50 (m, 4H), 2.32 (m, 2H), 3.62
 15 (m, 2H), 4.91 (dd, 1H), 5.22 (d, 2H), 7.31 (m, 5H),
 7.77 (m, 2H), 7.86 (m, 2H) ppm

¹³C-NMR (CDCl₃): 22.62, 28.46, 31.91, 52.32, 62.32,
 67.46, 123.55, 128.06, 128.31, 128.53, 131.77,
 20 134.23, 135.28, 167.76, 169.25 ppm

B(3).



25 To a stirred and chilled (-78°C, Dry ice-IPA
 bath) oxalyl chloride solution (2.0 M solution in
 CH₂Cl₂, 16.3 ml, 32.6 mmole) under argon was added
 dropwise a solution of dimethyl sulfoxide (4.64 ml,
 65.32 mmole) in dry CH₂Cl₂ (10 ml). After the

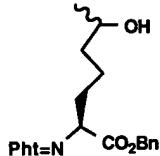
addition was complete, the solution was stirred at -78° for 15 minutes, then treated with a solution of Part B(2) compound (10g, 27.22 mmole) in dry CH₂Cl₂ (70 ml), stirred at -78° for another 15 minutes and
5 slowly treated with triethylamine (16 ml). The resulting solution was stirred at -78° for 15 minutes, gradually warmed up to 0°, poured into 1:1 EtOAc-Et₂O (500 ml), washed with 1.0 N HCl solution, water and brine, dried over anhydrous Mg₂SO₄ and
10 evaporated in vacuo to afford title compound (10 g) as a light yellow oil in 100% yield.

H¹-NMR (CDCl₃): δ = 1.66 (m, 2H), 2.40 (m, 4H), 4.90 (dd, 1H), 5.18 (d, 2H), 7.35 (m, 5H), 7.74 (m, 2H),
15 7.86 (m, 2H), 9.72 (s, 1H) ppm

C¹³-NMR (CDCl₃): 18.66, 27.99, 42.87, 51.83, 67.47, 123.50, 128.00, 128.26, 128.44, 131.58, 134.21, 135.04, 167.55, 168.80, 201.31 ppm

20

B(4).



A stirred and chilled (0°C, ice bath) solution
25 of Part B(3) compound (10.1 g, 27.64 mmole) in dry CH₂Cl₂ (100 ml) under argon was treated with a solution of trimethylaluminum (2.0 M solution in hexane, 23.4 ml, 46.8 mmole). The resulting solution was stirred for 45 minutes, quenched with 100 ml of a
30 saturated NH₄Cl solution (foaming) and partitioned between 1:1 Et₂O-water (400 ml). The organic layer

was separated and the aqueous layer was re-extracted with EtOAc (2x150 ml). The organic extracts were combined, washed with brine, dried over anhydrous Mg₂SO₄ and evaporated in vacuo to afford title

5 compound (10.3 g) as a gum in 98.7% yield.

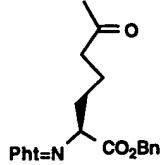
TLC: Silica gel, 6:4 EtOAc-hexane, R_f = 0.42, UV and PMA.

10 H¹-NMR (CDCl₃): δ = 1.12 (d, 3H), 1.43 (m, 4H), 3.73 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.76 (m, 2H), 7.86 (m, 2H) ppm

C¹³-NMR (CDCl₃): 22.5, 23.40, 28.47, 28.59, 38.20,

15 38.34, 52.20, 67.35, 67.51, 123.43, 127.94, 128.19, 128.41, 131.65, 134.11, 135.16, 167.62, 167.67, 169.13 ppm

B(5).



To a stirred and chilled (-78°C, Dry ice-IPA bath) oxallyl chloride solution (2.0 M solution in CH₂Cl₂, 257.3 ml, 514.6 mmole) under argon was added
 25 CH₂Cl₂ (300ml). To this solution, a solution of dimethyl sulfoxide (80.4 g, 1.03 mole) in dry CH₂Cl₂ (30 ml) was added dropwise. After the addition was complete, the reaction mixture was stirred at -78° for 20 minutes, treated with a solution of Part B(4)
 30 compound (151 g, 395.88 mmole) in dry CH₂Cl₂ (700 ml), stirred at -78°C for another 20 minutes and slowly treated with triethylamine (300 ml). The

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resulting solution was stirred at -78° for 15 minutes, gradually warmed up to 0°, poured into 1:1 EtOAc-Et₂O (3 L), washed with 1.0 N HCl solution, water and brine, dried over anhydrous Mg₂SO₄ and 5 evaporated in vacuo to afford title compound (149.4 g) as a yellow oil in 99.5% yield.

TLC: Silica gel, 6:4 EtOAc-hexane, R_f=0.5, UV and PMA.

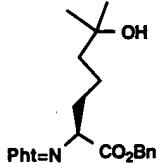
10

¹H-NMR (CDCl₃): δ = 1.60 (m, 2H), 2.10 (s, 3H), 2.26 (m, 2H), 2.47 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.84 (m, 2H) ppm

15

¹³C-NMR (CDCl₃): 20.15, 27.93, 29.84, 42.47, 51.89, 67.40, 123.46, 127.97, 128.23, 128.43, 131.61, 134.17, 135.10, 167.57, 168.93, 207.80 ppm

B(6).



20

A chilled (-78°C, Dry ice-IPA Bath) and stirred solution of titanium(IV) chloride (112.05 g, 590.65 mmole) in CH₂Cl₂ (1.5 L) under argon was 25 treated with methylmagnesium chloride (3 M solution in THF, 196.9 ml, 590.65 mmole). The black solution was allowed to warm up to -35°C and a solution of Part B(5) compound (149.4g, 393.77 mmole) was added dropwise. After the addition was complete, the 30 resulting solution was allowed to warm up to 0°C, stirred at 0°C for 2 hours and quenched with

saturated NH₄Cl solution. The CH₂Cl₂ layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2x700 ml). The CH₂Cl₂ extracts were combined, washed with brine, dried over anhydrous Mg₂SO₄ and 5 evaporated in vacuo. The black residue was passed through a pad of silica gel (E. Merck, 230-400 mesh, 900 g) eluting with EtOAc-hexane (1:1) to afford a tlc-homogeneous title compound (144.8 g) as a yellow oil in 93% yield.

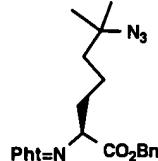
10

TLC: Silica gel, 1:1 EtOAc-hexane, R_f=0.4, UV and PMA.

H¹-NMR (CDCl₃): δ=1.14 (s, 6H), 1.45 (m, 4H), 2.30 15 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 7.74 (m, 2H), 7.86 (m, 2H) ppm

C¹³-NMR (CDCl₃): 20.88, 29.00, 29.17, 42.78, 52.13, 67.35, 70.47, 123.44, 127.95, 128.19, 128.41, 131.66, 20 134.11, 167.66, 169.14 ppm

B(7).



25 A stirred solution of Part B(6) compound (44.3 g, 364.89 mmole) and azidotrimethylsilane (63.06 g, 547.34 mmole) in dry CH₂Cl₂ (2.2 L) at room temperature under argon was treated with boron trifluoride diethyl etherate (67.32 g, 474.36 mmole). 30 After being stirred for 5 days, the resulting solution was quenched with water (1.5 L). The

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organic layer was separated, washed with saturated NaHCO₃ solution, water and brine, dried over anhydrous Mg₂SO₄ and evaporated in vacuo. The residue was chromatographed on a column of silica gel (E. Merck, 230-400 mesh, 700 g) eluting with EtOAc-hexane (1:3) to afford a tlc-homogeneous title compound (124.9 g) as a light yellow oil in 81.3% yield.

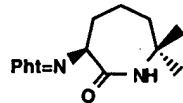
10 TLC: Silica gel, 3:7 EtOAc-hexane, R_f=0.5, UV and PMA.

H¹-NMR (CDCl₃): δ=1.20 (s, 6H), 1.45 (m, 4H), 2.30 (m, 2H), 4.90 (dd, 1H), 5.19 (d, 2H), 7.30 (m, 5H), 15 7.74 (m, 2H), 7.86 (m, 2H) ppm

C¹³-NMR (CDCl₃): 20.97, 25.67, 25.92, 28.80, 40.53, 52.02, 61.16, 67.40, 123.47, 127.97, 128.23, 128.43, 131.66, 134.14, 135.12, 167.60, 169.01 ppm

20

B(8).



A solution of Part B(7) compound (124.8 g, 25 296.81 mmole) and 10% Pd/C (32g) in dry DMF (2.0 L) was hydrogenated for 24 hours. After completion, argon was bubbled through the reaction mixture to remove excess hydrogen and methyl sulfide (2.6 ml) was added to poison the palladium. To this solution 30 1-hydroxybenzotriazole hydrate (46.74 g) was added and followed by ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride salt (68.74 g). The resulting solution was stirred at room temperature

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under argon for 3.5 hours, diluted with EtOAc (2 L) and filtered through a pad of celite. The filtrate was washed with 0.5 N HCl solution, saturated NaHCO₃ solution, and brine, dried over anhydrous Mg₂SO₄ and 5 evaporated in vacuo to give a gum. This was triturated with Et₂O-hexane (2:1) to afford a tlc-homogeneous title compound (74.5 g) as a white solid in 87.7% yield.

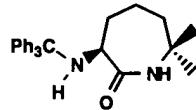
10 TLC: Silica gel, 3:7 EtOAc-CH₂Cl₂, R_f=0.35, UV and PMA.

H¹-NMR (CDCl₃): δ=1.30 (s, 3H), 1.45 (s, 3H), 1.74 (m, 2H), 1.96 (m, 3H), 2.74 (m, 1H), 4.98 (d, 1H), 15 6.00 (s, 1H), 7.20 (m, 2H), 7.85 (m, 2H) ppm

C¹³-NMR (CDCl₃): 23.89, 26.65, 29.58, 33.32, 40.68, 52.69, 54.51, 123.34, 123.15, 133.87, 168.06, 171.03 ppm

20

B(9).



A stirred solution of Part B(8) compound (74.5 25 g, 260.19 mmole) in a mixture of CH₃OH (900 ml) and CH₂Cl₂ (250 ml) at room temperature under argon was treated with hydrazine monohydrate (18.24 g, 364.26 mmole). After 48 hours, the solid was filtered off and the filtrate was evaporated in vacuo to give a 30 solid (41 g).

To a stirred solution of the above solid (41 g) in CH₂Cl₂ (2 L) at room temperature under argon was added triethylamine (50 ml) and triphenylmethyl

chloride (83.41 g). After 1.5 hours, the resulting slurry was diluted with EtOAc, washed with water and brine, dried over anhydrous Mg₂SO₄ and evaporated in vacuo to give a gum. This was triturated with Et₂O-

5 pentane to give title compound (100.1 g) as a white solid in 96.5% yield.

TLC: Silica gel, 6:4 EtOAc-hexane, R_f=0.53, UV and PMA.

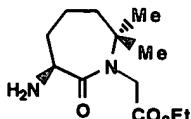
10

H¹-NMR (CDCl₃): δ=1.00 (s, 3H), 1.10 (s, 3H); 1.46 (m, 6H), 3.36 (m, 1H), 4.03 (m, 1H), 5.20 (d, 1H), 6.00 (s, 1H), 7.20 (m, 2H), 7.85 (m, 2H) ppm

15

C¹³-NMR (CDCl₃): 22.86, 25.81, 33.50, 34.23, 40.16, 51.97, 55.60, 71.89, 126.22, 127.61, 128.96, 146.48, 176.71 ppm

B(10).



20

To a stirred solution of Part B(9) compound (50 g, 125 mmole) in dry THF (1020 ml) at room temperature under argon was added simultaneously (at same rate) a solution of lithium bis(trimethylsilyl)-amide (1.0 M solution in THF, 627.3 ml, 627.3 mmole) and a solution of ethyl bromoacetate (104.8 g, 627.3 mmole) in THF (523 ml) over the period of 1.0 hour. After the addition was complete, the solution was stirred for 30 hours, quenched with saturated NH₄Cl solution (1.0 liter) and extracted with EtOAc (3x700 ml). The EtOAc extracts were combined, washed with

saturated NaHCO₃ solution and brine, dried over anhydrous Mg₂SO₄ and evaporated in vacuo to afford a black oil. The experiment was repeated on the same scale to give a similar result. The combined black
5 oils was chromatographed on a column of silica gel (E. Merck, 230-400 mesh, 1.6 kg) eluting with EtOAc-hexane (1:4) to give a light yellow oil. This was dissolved in dry CH₂Cl₂ (2 L) and treated with trifluoroacetic acid (78 ml). The solution was
10 stirred at room temperature under argon for 1.0 hour and then evaporated in vacuo at 30°. The residue was diluted with 1.0 N HCl solution (400 ml) and washed with Et₂O (2x400 ml). The aqueous was carefully neutralized to pH=7-8 with solid NaHCO₃ (foaming) and
15 extracted with CH₂Cl₂ (3x1.2 L). The CH₂Cl₂ extracts were combined, dried over anhydrous Na₂SO₄ and evaporated in vacuo to afford a tlc homogeneous title compound (51.5 g) as a light brown oil in 84.7% yield.

20

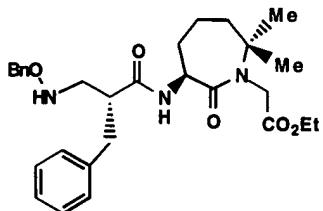
TLC: Silica gel, 8:1:1 CH₂Cl₂-CH₃OH-AcOH, R_f=0.3,
PMA and Ninhydrin.

H¹-NMR (CDCl₃): d=1.28 (t, 3H), 1.36 (s, 3H), 1.38
25 (s, 3H) 1.60 (m, 1H), 1.90 (m, 5H), 3.75 (m, 1H),
4.00 (d, 1H), 4.22 (q, 2H), 4.28 (d, 2H) ppm

C¹³-NMR (CDCl₃): 14.00, 20.06, 28.19, 30.07, 32.29,
39.98, 46.87, 53.20, 58.38, 60.73, 170.35, 177.06 ppm

30

C.

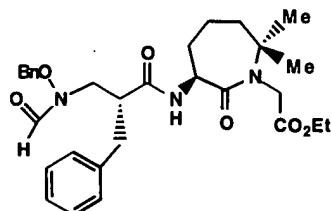


Part A compound (641 mg, 1.42 mmol) was

5 partitioned between EtOAc and 5% KH₂PO₄ (adjusted to pH 2.5 with H₃PO₄). The layers were separated and the aqueous layer was back-extracted with EtOAc. The pooled EtOAc extracts were washed with brine, dried (Na₂SO₄), filtered and stripped to give an oil
10 (assume 1.42 mg). The oil was dissolved in CH₂Cl₂ (10 mL) and the resulting solution was treated with Part B amine (364 mg, 1.50 mmol) in CH₂Cl₂ (2 mL) and cooled to 0°C. The mixture was subsequently treated with HOBT hydrate (195 mg) followed by EDAC (285 mg, 1.48 mmol). After stirring at 0°C for 45 minutes and at room temperature for 45 minutes, the mixture was partitioned between EtOAc and 5% KH₂PO₄ (adjusted to pH 2.5 with H₃PO₄). The EtOAc extract was washed successively with H₂O, 50% saturated NaHCO₃ and
15 brine, then dried (Na₂SO₄), filtered and stripped. The residue was flash chromatographed (Merck SiO₂, 7/3-EtOAc/hexanes as eluant) to obtain title compound (427 mg, 59%, TLC R_f 0.37 (8/2-EtOAc/hexanes)) as a diastereomerically pure compound. In addition, the
20 minor diastereomer was isolated from the column (66 mg, 9%, TLC R_f 0.27 (8/2-EtOAc/hexanes)). NMR of this material was consistant with an isomer of the title compound.
25

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D.

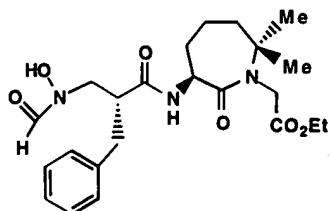


Acetic anhydride (500 μ L) was added to formic acid (5.0 mL) at 0°C and the mixture was stirred for 30 minutes. Approximately 2.6 mL of this solution was added to a solution of Part C compound (208 mg, 0.413 mmol) in THF (1.1 mL) at 0°C. After 30 minutes, most of the solvent was removed by rotary evaporation and the residue was partitioned between EtOAc and saturated NaHCO₃. The EtOAc extract was washed with brine, dried (Na₂SO₄), filtered and stripped to give title compound (216 mg, 97%) as an oily foam which was used directly in the next reaction without further purification.

TLC R_f 0.37 (EtOAc)

HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90% H₂O-10% MeOH-0.2% H₃PO₄; solvent B: 0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R = 17.2 min (100%).

E.

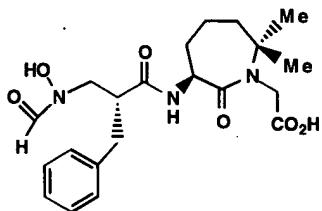


A solution of Part D compound (216 mg, 0.402 mmol) in absolute EtOH (5 mL) was hydrogenated (balloon) over 10% Pd/C (33 mg) at room temperature for 2 hours. The mixture was filtered through Celite, stripped, and azeotroped twice with EtOAc/Et₂O/hexanes to give title compound (174 mg, 97%) as an off-white foam.

TLC R_f 0.33 (5/95-HOAc/EtOAc)
 HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90%H₂O-10% MeOH-0.2% H₃PO₄; solvent B: 0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R = 12.8 min (100%).

20

F.



A stirred solution of Part E compound (168 mg, 0.376 mmol) in MeOH (3 mL) at room temperature was treated with aqueous 1 N NaOH (3 mL). An additional

portion of aqueous 1 N NaOH (3 mL) was added after 3.5 hours. After a total of 6 hours, the mixture was made acidic with 5% KHSO₄ and extracted twice with EtOAc. The EtOAc extract was washed with brine,

5 dried (Na₂SO₄), filtered and stripped. The residue was dissolved in a small amount of MeOH and EtOAc and triturated with Et₂O/hexanes to give title compound (134 mg, 86%) as an off-white solid/foam ([a]_D = +18.0° (c 0.5, CH₂Cl₂)).

10

TLC Rf 0.10 (5/95-HOAc/EtOAc)

HPLC YMC S3 ODS column (6.0 x 150 mm); eluted with B:A solvent mixture, 40 to 100% B over a 20 minute linear gradient (solvent A: 90%H₂O-10% MeOH-0.2%

15 H₃PO₄; solvent B:0% H₂O-90% MeOH-0.2% H₃PO₄); flow rate 1.5 mL/min detecting at 220 nm; t_R = 9.00 min (>97.4%).

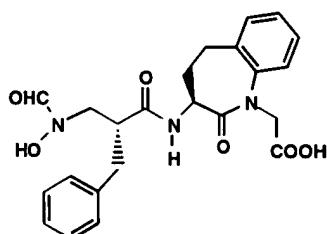
Anal. Calc'd for C₂₁H₂₉N₃O₆•0.75H₂O•0.3Et₂O

20 C, 58.57; H, 7.42; N, 9.23

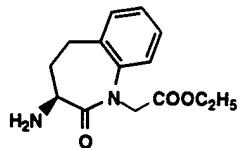
Found C, 58.31; H, 7.20; N, 8.99.

Example 4

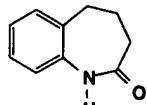
25 [S-(R*,R*)]-3-[[3-(Formylhydroxyamino)-1-oxo-2-(phenylmethyl)propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepine-1-acetic acid



A.



A(1).



5

Solid sodium azide (26.0 g., 0.2 mole) was introduced into a 3-neck round-bottom flask with an overhead stirrer, made into a paste with warm water (26 ml), layered with chloroform (160 ml) and cooled down to 0° (ice-salt bath). The mixture was treated dropwise with concentrated sulfuric acid (11.2 ml, 0.5 eq.) over a period of 10 minutes, stirred for an additional 10 minutes then decanted into a flask containing anhydrous sodium sulfate. The dried solution was filtered through a glass wool plug in a funnel into a 500-ml round-bottom flask. Titration of an aliquot (1.0 ml) with 1.0 N NaOH using phenolphthalein as an indicator gave a normality of 1.7 N for the hydrazoic acid.

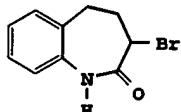
Tetralone (15.94 g, 0.108 mole) was added to the hydrazoic acid solution (0.136 mole or 1.25 eq.), heated to 40-45° (oil bath) then treated dropwise with 36.0 N H₂SO₄ (28.7 ml, 5 eq.) over a period of 1.0 hour. (Intense bubbling took place with each drop added for the first 30 minutes). The reaction mixture was cooled down to room temperature, poured into H₂O (720 ml) and stirred for 5 minutes. The solution was then extracted with EtOAc (3 x 250 ml) and the combined organic extracts were washed with

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brine (100 ml), dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried *in vacuo*. The crude product (17.819 g) was recrystallized from CH₂Cl₂ (70 ml) and Hexane (400 ml) to give title compound as off-white precipitates (10.017 g, m. pt. 138-140°C) with consistent ¹H-NMR and ¹³C-NMR spectral data.

The mother liquor was chromatographed on a silica gel column (Merck, 240 g), eluting the column with EtOAc:Hexane (1:4) to give an additional amount of 5.058 g (total yield= 15.075 g, 85.6 %).
TLC: R_f 0.37 (Silica gel; EtOAc:Hexane-1:1; UV).

A(2).

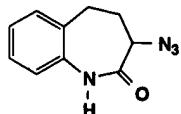


A solution of Part A(1) compound (1.0 g, 6.20 mmoles) in dry CHCl₃ (15 ml) was cooled down to 0°C (ice-salt bath), treated with PCl₅ (1.5 g, 7.20 mmoles) followed by I₂ (15 mg) then stirred at 0°C under argon for 30 minutes. The yellow solution was treated with Br₂ (0.39 ml or 1.2 g, 7.51 mmoles), warmed up to room temperature and refluxed under argon for 4.0 hours. The mixture was then poured into ice-water (20 g), stirred and the phases were separated, washing the aqueous phase with CHCl₃ (25 ml). The combined organic extracts were washed with H₂O (5.0 ml), dried (anhydrous MgSO₄), filtered, evaporated to dryness and dried *in vacuo*. The crude product mixture was chromatographed on a silica gel column (Merck, 70 g), eluting the column with EtOAc:Hexane (1:9) to give title compound as off-white precipitates (1.137 g., m.pt. 170-172°, 70.1 %)

with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data.
 TLC: R_f 0.13 (Silica gel; EtOAc:Hexane -1:4; UV).

A(3).

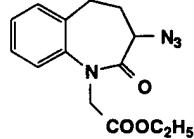
5



A solution of Part A(2) compound (936 mg, 3.9
 mmoles) and NaN_3 (300 mg, 4.6 mmoles) in dry
 dimethylsulfoxide (20 ml) was stirred at 60° (oil
 bath) under argon for 6.0 hours. The reaction
 mixture was cooled down to room temperature, poured
 into cold water (125 ml), stirred for 15 minutes and
 filtered, washing the solids formed with water. The
 crude product was dried *in vacuo* at 60° over drierite
 for 24 hours to give title compound (725 mg, m.pt.
 $150-152^\circ$, 91.9 %) as an off-white solid with
 consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data.
 TLC: R_f 0.58 (Silica gel; EtOAc:Hexane- 1:4 then 1:1;
 UV).

20

A(4).

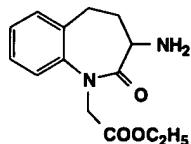


A solution of Part A(3) compound (10.858 g,
 25 53.7 mmoles) in dry tetrahydrofuran (100 ml) was
 treated with Bu_4NBr (1.791 g, 5.56 mmoles) and
 powdered KOH (3.937 g, 70.2 mmoles) followed by ethyl
 bromoacetate (6.8 ml, 61.3 mmoles). The reaction
 mixture was stirred at room temperature under argon
 30 for 1.5 hours then partitioned between H_2O (196 ml)

and CH_2Cl_2 (2×375 ml). The combined organic extracts were washed with H_2O (2×196 ml) and brine (100 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness and dried *in vacuo*. The crude product was combined with the crude product mixture from a previous run (2.936 g, 12.86 mmole scale) and chromatographed on a silica gel column (Merck), eluting the column with Toluene:EtOAc (98:2) and EtOAc:Hexane (1:9) to give title compound as a solid (15.48 g, 93.5%)¹ with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data.
TLC: R_f 0.63 (Silica gel; EtOAc:Hexane- 1:2; UV).

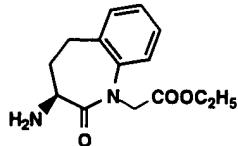
A(5).

15



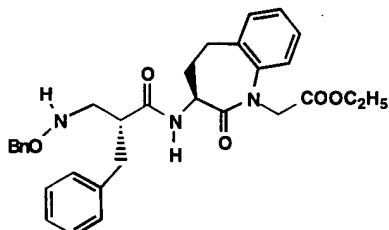
A solution of Part A(4) compound (8.95 g, 31.0 mmoles) in absolute ethanol (50 ml) was treated with 10% Pd/C (443 mg) and hydrogenated at 45 psi for 3.5 hours, venting the Parr bottle every 30 minutes for the first 1.5 hours. The mixture was filtered through a Celite® pad in a millipore unit, washing the pad well with absolute ethanol (3 x 50 ml). The clear filtrate was evaporated to dryness and dried *in vacuo* to give title compound as a thick yellow syrup (7.929 g, 97.5%) with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. TLC: R_f 0.45 (Silica gel; $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ - 9:1; UV).

A(6).



A solution of Part A(5) compound (14.8 g,
 5 56.4 mmoles) and L-tartaric acid (8.50 g) in hot
 absolute ethanol (118 ml) was kept overnight at 0°,
 at room temperature for 3 days and then at 0° for
 another 2 days. The solid that formed was
 recrystallized from absolute ethanol (118 ml) two
 10 more times until a consistent specific rotation was
 obtained. The precipitates (6.319 g) from the second
 recrystallization was then suspended in EtOAc (100
 ml), treated with 10% NH₄OH (12 ml) and stirred for 5
 minutes. The organic phase was separated, washed
 15 with 10% NH₄OH (10 ml) and brine (15 ml), dried
 (anhydrous Na₂SO₄), filtered, evaporated to dryness
 and dried in vacuo to give title compound as a white
 solid (3.927 g, m.pt. 105-107°, 26.5%) with
 consistent ¹H-NMR and ¹³C-NMR spectral data.
 20 [α]_D = -277° (c 0.99, EtOH). TLC : R_f 0.45 (Silica
 gel; CH₂Cl₂:CH₃OH- 9:1; UV).

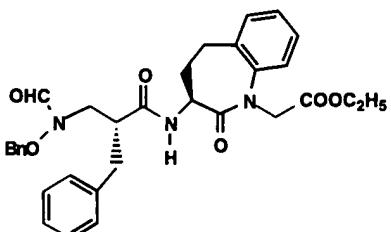
B.



Example 3 Part A ephedrine salt (414 mg, 0.93 mmole), was partitioned between 5 % KH₂PO₄ (adjusted to pH 2.5; 4.0 ml) and EtOAc (2 x 20 ml) and the combined organic extracts were washed with brine (4.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo to give the free acid of the Example 4 Part A compound as a clear syrup (286.6 mg, 100 % crude yield).

A solution of the above free acid (286.6 mg, 0.93 mmole) in dry CH₂Cl₂ (6.0 ml) was cooled to 0°C (ice-salt bath) and treated sequentially with a solution of the above free amine (271 mg) in dry CH₂Cl₂, HOBT·H₂O (126.1 mg, 0.93 mmole) and EDAC (185.4 mg, 0.97 mmole). The reaction mixture was stirred at 0°C for 1.0 hour, at room temperature for 2.0 hours, then partitioned between EtOAc (2 x 20 ml) and H₂O (4.0 ml). The organic extracts were washed with 5% KH₂PO₄ (adjusted to pH 2.5; 4.0 ml), H₂O (4.0 ml), saturated NaHCO₃ (4.0 ml) and brine (4.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo. The crude product was chromatographed on a silica gel column (Merck, 70 g.), eluting the column with EtOAc:Hexane mixtures (1:3; 1:1) to give pure title compound (202 mg) and impure product. A second chromatography gave title compound as a syrup (total of 292.1 mg, 59.3%) with consistent ¹H-NMR and ¹³C-NMR spectral data. TLC: R_f 0.32 (Silica gel; EtOAc:Hexane -1:1; UV).

C.

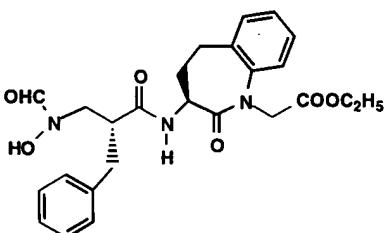


A cooled solution of HCOOH (5.0 ml) was

- 5 treated with acetic anhydride (Ac_2O) (0.5 ml) and stirred at 0°C for 30 minutes. A solution of Part B compound (288 mg, 0.54 mmole) in dry THF (1.5 ml) was cooled to 0°C (ice-salt bath), treated with the above $\text{Ac}_2\text{O}/\text{HCOOH}$ mixture (3.4 ml) and stirred at 0°C for
- 10 1.0 hour. The reaction mixture was evaporated to dryness and the residual syrup was dissolved in EtOAc (40 ml), washed with saturated NaHCO_3 (5.0 ml) and brine (5.0 ml), dried (anhydrous Na_2SO_4), filtered, evaporated to dryness, evaporated from toluene and
- 15 dried in vacuo to give title compound as a syrup (311.3 mg, 100 % crude) with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data. TLC: R_f 0.18 (Silica gel; EtOAc:Hexane (1:1; UV).

20

D.



A solution of Part C compound (311 mg) in CH_3OH (10 ml) was treated with 10% Pd/C (53 mg) and

hydrogenated (balloon) at room temperature for 2.0 hours. The reaction mixture was diluted with CH₃OH (10 ml) and filtered through a Celite® pad in a millipore unit, washing the pad well with CH₃OH (3 x

5 10 ml). The clear filtrate was evaporated to dryness and dried *in vacuo* to give title compound as a syrup (256.7 mg, 100% crude) with consistent ¹H-NMR and ¹³C-NMR data. TLC: R_f 0.25 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV).

10

E. [S-(R*,R*)]-3-[3-(Formylhydroxyamino)-1-oxo-2-(phenylmethyl)propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-benzazepine-1-acetic acid

A solution of Part D compound (256.7 mg) in 15 CH₃OH (3.5 ml) was treated with 1.0 N NaOH (2.17 ml, 4 eq) and stirred at room temperature for 1.0 hour under argon. The reaction mixture was brought to pH 1.0 with 5% KHSO₄ (9.45 ml), extracted with EtOAc (40 ml) and the organic extract washed with brine (5.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried *in vacuo*. The crude product was triturated with CH₂Cl₂:Hexane (1:4-25 ml) and hexane (20 ml) then dried *in vacuo* to give title compound as an amorphous off-white solid (215.6 mg, 90.4%) 20 with consistent MS, IR, ¹H-NMR and analytical data. 25 TLC: R_f 0.30 (Silica gel; EtOAc:HOAc- 95:5; UV).

[α]_D = -332.8° (c 0.558, CH₃OH)

HPLC: t_R = 5.21 min (95.8% R isomer); t_R = 9.58 min

30 (3.59% S isomer); YMC S3 ODS-A 150 x 6 mm; 220 nm, flow rate = 1.5 ml/min; 56% (10% H₂O- 90% CH₃OH- 0.2% H₃PO₄)/44% (90% H₂O- 10% CH₃OH- 0.2% H₃PO₄), isocratic.

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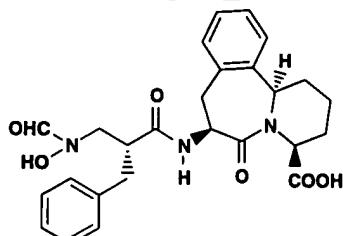
Anal. Calc'd for C₂₃H₂₅N₃O₆:

C, 62.86; H, 5.73; N, 9.56

Found: C, 62.88; H, 5.98; N, 9.20.

5

Example 5



A.



10

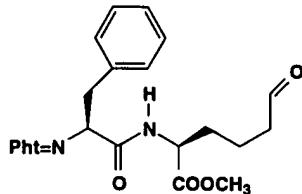
A solution of L-hydroxynorleucine (2.0 g, 13.6 mmoles) in dry methanol (70 ml) was saturated with HCl gas until a clear yellow solution was obtained. The reaction mixture was cooled to room temperature, 15 stirred for 2.0 hours, evaporated to dryness, evaporating the syrup once from toluene (100 ml) then evaporated in vacuo to give the ester as a yellow oil. The crude ester was dissolved in dry CH₂Cl₂ (50 ml) and dry DMF (15 ml), treated with NMM (2.5 ml, 20 22.7 mmoles) and cooled to 0°C (ice-salt bath). The mixture was treated with N-phthaloyl-L-phenyl-alanine (4.0 g, 13.6 mmoles), HOBt·H₂O (1.89 g, 13.99 mmoles) and EDAC (2.87 g, 14.98 mmoles), stirred at 0°C for 25 minutes and at room temperature for 2.0 hours.

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The reaction mixture was partitioned between EtOAc (2 x 200 ml) and H₂O (60 ml) and the combined organic extracts were washed sequentially with 0.5 N HCl (60 ml), H₂O (60 ml), 1/2 saturated NaHCO₃ (60 ml) and brine (60 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried *in vacuo*. The crude product mixture was chromatographed on a silica gel column (Merck, 200 g), eluting the column with EtOAc to give the desired product as a syrup (4.0 g). An additional 321 mg was obtained on re-chromatography of the impure fractions to give title compound (4.32 g, 73%) with consistent ¹H-NMR and ¹³C-NMR spectral data.
TLC: R_f 0.43 (Silica gel; EtOAc; UV).

15

B.

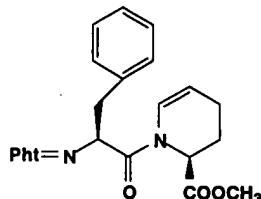


A solution of oxalyl chloride (1.02 ml, 11.7
20 mmoles) in dry CH₂Cl₂ (56 ml), was cooled to -78°C
(dry-ice-acetone bath), treated with a solution of
dry DMSO (1.67 ml, 21.6 mmoles) in CH₂Cl₂ (2.0 ml)
and stirred at -78°C for 20 minutes. The mixture was
treated with a solution of Part A compound (4.29 g,
25 9.78 mmoles) in dry CH₂Cl₂ (22 ml), stirred at -78°C
for another 15 minutes, then treated with triethyl-
amine (8.4 ml). The reaction mixture was stirred at
-78°C for 5.0 minutes, allowed to come to room
temperature over a period of 45 minutes, then
30 partitioned between EtOAc (200 ml) and 0.5 N HCl (2 x

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20 ml). The organic phase was washed with brine (40 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo to give title compound as a thick syrup (4.428 g, 100% crude yield), with
 5 consistent ¹H-NMR and ¹³C-NMR spectral data.
 TLC: R_f 0.73 (Silica gel; EtOAc; UV).

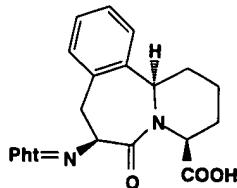
c.



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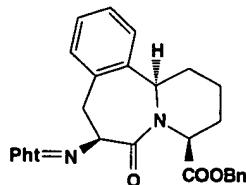
A mixture of Part B compound (4.428 g, 9.78
mmoles) and TFA (0.20 ml, .2.6 mmoles) in dry CH₂Cl₂
(62 ml) was refluxed under argon for 2.0 hours. The
reaction mixture was cooled to room temperature,
washed with 1/2 saturated NaHCO₃ (20 ml) and brine
(20 ml), dried (anhydrous Na₂SO₄), filtered,
evaporated to dryness and dried in vacuo. The crude
product mixture was chromatographed on a silica gel
column (Merck, 200 g), eluting the column with
CH₂Cl₂:EtOAc (9:1) to give the desired product as a
syrup. The syrup was triturated with Et₂O:Hexane
(2:1-60 ml) to give title compound as a white
precipitate (2.92 g, 72%; m.p. 141-143°C) with
consistent ¹H-NMR and ¹³C-NMR spectral data.
TLC: R_f 0.67 (Silica gel; CH₂Cl₂:EtOAc-9:1; UV).

D.



A solution of Part C compound (2.923 g, 6.99
 5 mmoles) in dry CH_2Cl_2 (14 ml) was treated with
 triflic acid (4.15 ml, 6.7 eq) and the resulting
 yellow solution was stirred at room temperature for
 20 hours. The reaction mixture was then poured into
 ice-water (100 ml), extracted with EtOAc (3×100 ml)
 10 and the combined organic extracts washed with H_2O (2×25 ml) and brine (25 ml), dried (anhydrous Na_2SO_4),
 filtered, evaporated to dryness and dried *in vacuo*.
 The crude product mixture was chromatographed on a
 silica gel column (Merck), eluting the column with
 15 $\text{EtOAc}:\text{Hexane}$ mixtures (1:1; 2:1) and $\text{EtOAc}:\text{HOAc}$
 (100:1). The desired fractions were combined,
 evaporated to dryness and dried *in vacuo* to give
 impure title compound as a solid foam (1.238 g, 42%)
 with consistent $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral data.
 20 TLC : R_f 0.73 (Silica gel; $\text{EtOAc}:\text{HOAc}$ -95:5; UV).

E.

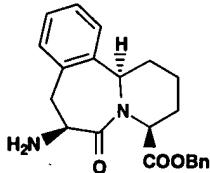


25 A solution of Part D compound (1.238 g, 3.06
 mmoles) in dry DMF (3.5 ml) was treated sequentially
 with benzyl bromide (0.35 ml, 2.94 mmoles) and Cs_2CO_3

(450 mg, 1.38 mmoles) then stirred at room temperature for 3.0 hours. The mixture was diluted with EtOAc (50 ml), washed with H₂O (5.0 ml), 0.5 N HCl (5.0 ml) and brine (5.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo. The crude product (1.63 g) was chromatographed on a silica gel column (Merck), eluting the column with EtOAc:Hexane (1:3) to give title compound as a syrup (586.4 mg, 39%) with consistent ¹H-NMR and ¹³C-NMR spectral data.

10 TLC: R_f 0.45 (Silica gel; EtOAc:Hexane-1:1; UV).

F.



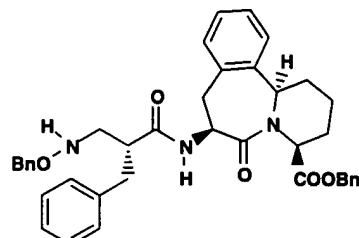
15

A solution of Part E compound (586 mg, 1.18 mmoles) in dry methanol (15 ml) was treated with NH₂NH₂•H₂O (66 µl, 1.2 eq) and stirred at room temperature for 48 hours. The reaction mixture was 20 diluted with Et₂O (50 ml) and filtered through a millipore unit, washing the solids well with Et₂O (40 ml). The clear solution was evaporated to dryness and the solids obtained were suspended in CH₂Cl₂ (90 ml) and the solution filtered through a millipore unit, washing the solids well with CH₂Cl₂ (40 ml). The combined organic extracts were washed with brine (15 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness and dried in vacuo to give title compound as a thick syrup (351 mg, 82 %) with a 30 consistent ¹H-NMR spectrum.

TLC: R_f 0.42 (CH₂Cl₂:MeOH-9:1; UV, Ninhydrin)

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G.

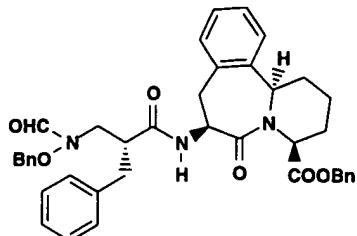


5 Example 3 Part A ephedrine salt (538 mg, 1.2
mmoles), was partitioned between 5% KH₂PO₄ (adjusted
to pH 2.5; 5.4 ml) and EtOAc (2 x 22 ml) and the
combined organic extracts were washed with brine (5.4
ml), dried (anhydrous Na₂SO₄), filtered, evaporated
10 to dryness and dried *in vacuo* to give the free acid
of the ephedrine salt as a clear syrup (323 mg, 100%
crude yield).

A solution of the free acid in dry CH₂Cl₂
(8.0 ml) was cooled to 0°C (ice-salt bath) and
15 treated sequentially with a solution of Part F
compound (351 mg, 0.96 mmole) in dry CH₂Cl₂ (2.0 ml),
HOBT•H₂O (163 mg, 1.2 mmoles) and EDAC (240 mg, 1.25
mmoles). The reaction mixture was stirred at 0°C for
1.0 hour, at room temperature for 1.5 hours, then
20 partitioned between EtOAc (40 ml) and H₂O (5.0 ml).
The organic extracts were washed with 5 % KH₂PO₄
(adjusted to pH 2.5; 5.0 ml), H₂O (5.0 ml), saturated
NaHCO₃ (5.0 ml) and brine (5.0 ml), dried (anhydrous
Na₂SO₄), filtered, evaporated to dryness and dried
25 *in vacuo*. The crude product (810 mg) was chromatographed
on a silica gel column (Merck), eluting the
column with EtOAc:Hexane (1:3) to give pure title
compound (494 mg, 65%) as a solid foam with
consistent ¹H-NMR and ¹³C-NMR spectral data.

TLC: R_f 0.45 (Silica gel; EtOAc:Hexane -1:1; UV).

H.

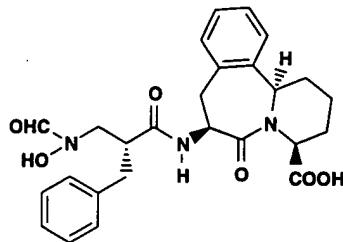


5

A cooled solution (0°C , ice-salt bath) of HCOOH (5.0 ml) was treated with Ac₂O (0.5 ml) and stirred at 0°C for 30 minutes. A solution of Part G compound (493 mg, 0.78 mmole) in dry THF (2.2 ml) was 10 cooled to 0°C (ice-salt bath), treated with the above Ac₂O/HCOOH mixture (4.9 ml) and stirred at 0°C for 1.5 hours. The reaction mixture was evaporated to dryness, evaporated from Et₂O (50 ml) and the residual syrup was dissolved in EtOAc (60 ml), washed 15 with saturated NaHCO₃ (7.0 ml) and brine (7.0 ml), dried (anhydrous Na₂SO₄), filtered, evaporated to dryness, evaporated from toluene and dried *in vacuo* to give title compound as a syrup (558.3 mg, 100 % crude) with consistent ¹H-NMR and ¹³C-NMR spectral 20 data.

TLC: R_f 0.2 (Silica gel; EtOAc:Hexane-1:1; UV).

I.



A solution of Part H compound (535 mg, 0.78 mmole) in CH₃OH (15 ml) was treated with 10 % Pd/C (83 mg) and hydrogenated (balloon) at room temperature for 4.0 hours. The reaction mixture was diluted with CH₃OH (15 ml) and filtered through a celite pad in a millipore unit, washing the pad well with CH₃OH (3 x 15 ml). The clear filtrate was evaporated to dryness and dried *in vacuo* to give a syrup (354.8 mg) which was triturated with CH₂Cl₂:Hexane (1:5-30 ml) and hexane (25 ml) then dried *in vacuo*. Title compound was obtained as an off-white solid foam (348.5 mg, 90%).

TLC: R_f 0.38 (Silica gel; CH₂Cl₂:MeOH- 9:1; UV).

MS (M+H)⁺ = 480

[α]_D = +44.6° (c 0.52, CH₃OH)

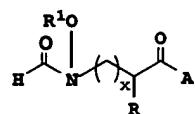
HPLC : t_R= 11.72 min (95.9%); YMC S3 ODS-A 150 x 6 mm; 220 nm, flow rate = 1.5 ml/min; 55% (10% H₂O- 90% CH₃OH- 0.2% H₃PO₄)/ 45% (90% H₂O- 10% CH₃OH- 0.2% H₃PO₄), isocratic.

Anal. Calc'd for C₂₆H₂₉N₃O₆•0.4 H₂O•0.14 Hexane (Eff. Mol. Wt. = 497.08):

C, 64.63; H, 6.83; N, 8.46

Found: C, 64.24; H, 6.43; N, 8.12

The following are examples of additional compounds of the invention which may be prepared employing procedures set out hereinbefore and in the 5 working Examples.



Example
No.

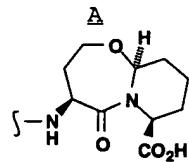
R^1

x

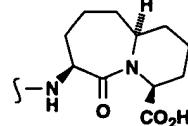
R

10

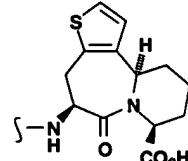
6 H 1 CH_2Ph



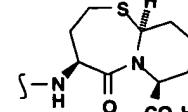
7 H 1 CH_2Ph



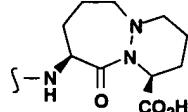
8 H 1 $CH_2CH(CH_3)_2$



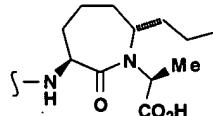
9 H 1 CH_2Ph



10 H 1 $CH_2CH(CH_3)_2$

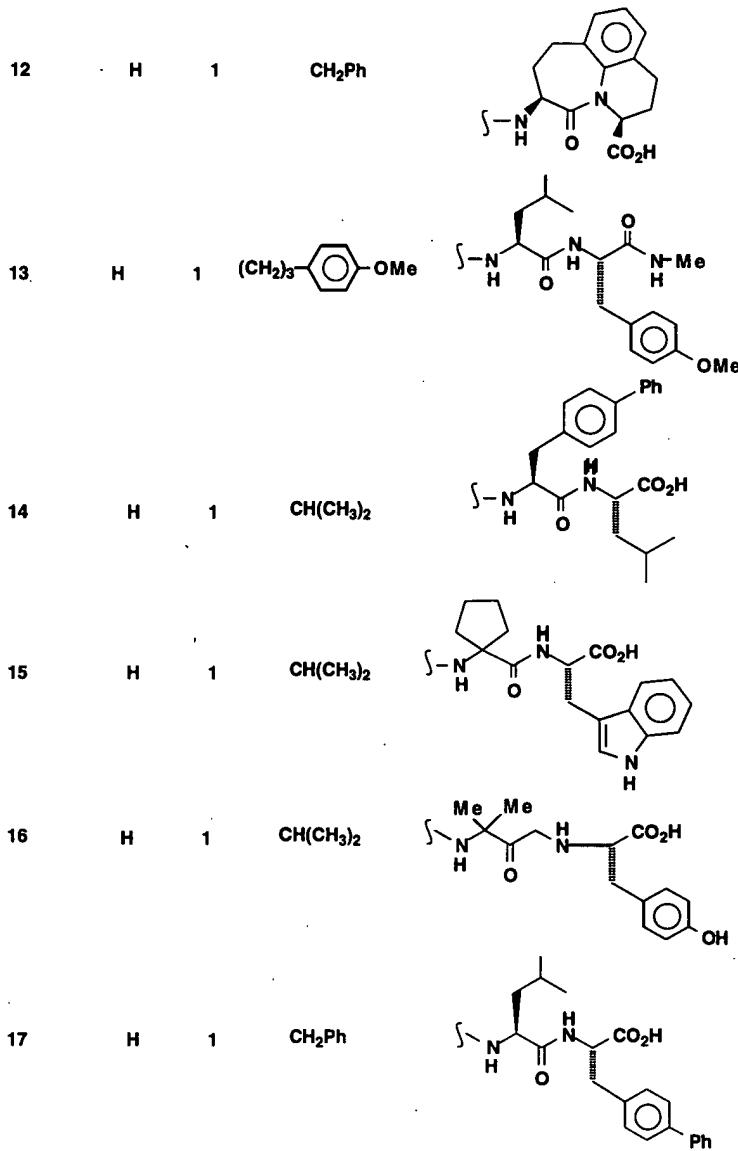


11 H 1 CH_2Ph



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